Acute kidney Injury in Children: Impacts and its Management

Quddus ASMR[1], Hasan MJ[2]

Abstract

The incidence of acute kidney injury (AKI) in children is increasing globally and is associated with increased mortality and long-term renal consequence.The definition of pediatric AKI was standardized for a more accurate assessment of the epidemiology of pediatric AKI. The definition of AKI is based on elevation in serum creatinine levels or decrease inurine output; accordingly, epidemiological studies have ensued. Recent advances in leveraging electronic medical health record systems and newbiomarkers appear to detect AKI earlier and predict prognosis more accurately than traditional markers have allowed for real-time risk stratification and prevention of pediatric AKI in the hospital setting. For high risk or early stage AKI patients, avoidance of nephrotoxins, optimization of blood pressure and volume status, sufficient nutritional support are necessary and have been demonstrated tobe effective in preventing the occurrence of AKI and improving prognosis. Lastly, renal replacement therapy is needed when conservative care fails. Further therapeutic innovation willdepend on improving the understanding of the basic mechanisms underlying AKI in children.

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Introduction

Kidney disease is now a global public health concern across the age spectrum, including in children. Acute kidney injury (AKI) (also referred to as acute renal failure) reflects a clinical presentations ranging from mild to severe injury that may result in permanent and complete loss of renal function. Acute kidney failure (AKF) in children is a catastrophic event. Acute kidney injury (AKI) can be defined as abrupt decline in renal excretory function, resulting in a decline in glomerular filtration rate (GFR), and impaired control of acid-base, electrolyte and fluid balance. Now AKI is a common problem, particularly in hospitalized children. The manifestation of AKI in children appears to be increasing and the etiology of AKI over the past decades has shifted from primary renal disease to multifactorial causes and it is an independent risk factor for increased mortality and severe morbidity.[1-2]

Renal injury can be divided into pre-renal disease, renal disease including vascular insults and post renal disease. The prognosis of AKF is highly dependent on the underlying etiology of the AKF. Children who suffered AKF from any cause are at risk of developing chronic kidney disease several years after the initial insult.[2]

Recently, many studies have been conducted in the field of pediatric AKI following adult studies and have prompted new interest.

Definition of AKI

There are several definitions have been used, most are based on the Risk, Loss of kidney function, Injury, Failure, End-stage renal disease (RIFLE) criteria, the subsequent pediatric RIFLE (pRIFLE) score and the Acute Kidney Injury Network (AKIN) criteria. Each of these definitions and stages for kidney injury slightly different, which made comparison studies and standardized recommendations regarding management more difficult.[3] In 2012, a standardized definition of AKI was proposed by the

1. *Prof. Dr. A.S.M. Ruhul Quddus; Professor (C.C), Department of Pediatrics, Community Based Medical College, Bangladesh*
2. *Dr. Mahmud Javed Hasan; Associate Professor and Head, Department of Nephrology Community Based Medical College, Bangladesh*

Address of correspondence:
Email: ruhulquddush@gmail.com
Mobile: 01712123225

Kidney Disease: Improving Global Outcomes (KDIGO) and has been validated in children and adults.[4] All are based on increase in serum creatinine from an established baseline or by the development of oliguria. The bloomers of a serum creatinine-based definition for AKI are well recognized including the

- influence of non-glomerularfiltration rate (GFR) determinants (e.g., musclemass, diet, hydration status);
- lack of sensitivity to acute, small changes in renal function; and
- excretion by routes other than filtration (proximaltubular secretion and bacterial degradation in the gastrointestinal tract)[17-18]

The severity of AKI is staged according to the amplitude of serum creatinine elevation form baseline value or the duration of compromised urine output. For neonates, the neonatal modified KDIGO definition was used in a recent large group (Table 1).[5-6] Even though it is based on a modification of the KDIGO definition, it is different with urinary output examine in 24 h. In addition, the baseline value is the lowest previous serum creatinine level because it reflects maternal creatinine in the first few days, declines physiologically within weeks of life at a rate that varies with gestational age.[41]

Table 1. Definitions and Staging of Kidney Disease: Improving Global Outcomes (KDIGO) and Neonatal Modified KDIGO Criteria for Acute Kidney Injury

Stage	Pediatric KDIGO criteria		Neonatal modified KDIGO criteria	
	Serum creatinine	Urine Output	Serum creatinine	Urine output
1	1.5-1.9 times baseline within 7 days	<0.5 mL/kg/h for 6-12 h	1.5-1.9 times baseline within 7 days	>0.5 and ≤ 1 mL/kg/h
	OR		OR	over 24 h
	≥ 0.3 mg/dL increase within 48 h		≥ 0.3 mg/dL increase within 48 h	
2	2.0-2.9 times baseline	<0.5 mL/kg/h for ≥ 12 h	2.0-2.9 times baseline	> 0.3 and ≤ 0.5 mL/kg/h
				over 24 h
3	≥3.0 times baseline	<0.3 mL/kg/h for ≥24 h	≥ 3.0 times baseline	≤ 0.3 mL/kg/h over 24 h
	OR	OR	OR	
	Increase in serum creatinine to ≥4.0 mg/dL	Anuria for ≥ 12 h	Increase in serum creatinine to ≥ 2.5 mg/dL	
	OR		OR	
	Initiation of renal replacement therapy		Initiation of renal replacement therapy	
	OR			
	Decrease in eGFR to <35 mL/min per 1.73 m^2			

Epidemiology

In recent years, epidemiological data revealing the financial cost and high morbidity and mortality associated with AKI have been reported in several studies on the subject involving pediatric patients.[8] However, contrasted with large scale adult epidemiologic studies, robust and broad based data in pediatrics is scanty.

In 2010, an epidemiological study involving a large number of pediatric patients was published, using the p-RIFLE for AKI diagnosis. 11% incidence of AKI has been demonstrated in patients between 31 days and 21 years of age admitted to a PICU in a single US center. A subsequent multi-center study in the same country described the incidence of 3.9 cases/1,000 hospitalizations and there was a need for artificial renal support (ARS) in 8.8% of the cases. This study also demonstrated higher mortality in the group requiring ARS (27.1% versus 14.2% $p < 0.001$).[9] In an assessment at a single center in New Zealand in the period 2001-2006, involving 226 children aged 0-14 years submitted to RRT and reported a mortality rate of 11%.[10]

Using the KDIGO classification available studies on the epidemiology of pediatric AKI in developing countries are mostly observational studies carried out in a single center. An exception is a study involving around 3.8 lac patients under the age of 18 years admitted to 27 Chinese hospitals,

which reported an incidence of AKI (AKIN) of 0.32% and a mortality rate of 3.4% in patients who developed AKI at any stage.[11] Mortality rates of 41.5%, 50.4%and 30% showed in studies in Nigeria, India, Thailand and Pakistan respectively.[12-15]

The Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology (AWARE) study described epidemiology of AKI. One study demonstrated that AKI developed in 26.9% of patients and KDIGO stage 2 or 3 AKI in 11.6% within 7 days of PICU admission.[40] AWARE is such a vital study that will inform the nephrology community of the prevalence and associations of AKI in pediatric patients.

Management and prevention of AKI

1. Risk factors:

As there are no effective medications for established AKI, prevention and early detection are the mainstays of management. Close monitoring of high-risk patients and reducing additional risk factors can prevent the occurrence of AKI. Prematurity and chronic diseases such as CKD render the patient susceptible to AKI and events such as volume depletion, exposure to nephrotoxins, sepsis, major surgery and critical illness lead to AKI.[16]

To predict AKI incritically ill children, the renal angina index was proposed on the basis of subtle kidney injury and patient risk factors such as ICU admission, stem cell transplantation, ventilation and inotropy.[19] Recently, a system using electronic health records was implemented and helped physicians detect AKI early and mitigate the influence of risk factors.[20] The system electronically reveals high-risk patients to the medical team in near real-time. As such, the medical team does not miss high-risk patients and monitors them carefully. It has been shown to improve the rate of recovery from AKI.[21]
For pediatric patients, this system was developed to screen children who experienced multiple nephrotoxin exposures, which prompted clinicians to monitor more closely for the development of AKI. It demonstrated a positive effect in decreasing exposure to multiple nephrotoxins and finally, AKI events.[22]

2. Supportive care

The supportive care comprises optimization of volume status, avoidance of nephrotoxic agents, blood pressure and nutritional support. It is recommended to maintain adequate renal perfusion through fluid and hemodynamic management.[23] Volume status should be optimal (i.e., not excessive, not insufficient). The previous medical cases and symptoms are important to evaluate volume status. Fluid intake, body weight,urine and stool output and vital signs should be monitored daily and lung sound and lower extremity edema should be checked.[24-25]
In the acute phase, fluid accumulation is common in the PICU, which is associated with high mortality in critically ill patients. The pediatric literature suggests that 10-20% fluid overload is a critical threshold at which outcomes are negatively impacted.[26-28]

Again, hypervolemic patients require further fluid restriction, urine output, omitting the replacement of insensible fluid losses and extrarenal losses while considering adequate nutritional support.[25] Diuretics therapy, especially loop diuretics, should be considered for hypervolemic patients. The pediatric literature shows that clinicians should consider initiating renal replacement therapy (RRT) at a fluid overload of >20%, while a fluid overload 10-20 % requires further evaluation.[28]

It is crucial for a patient to maintain optimal blood pressure. For patients with hypotension, fluid resuscitation is initially considered if hypotension is due even partially to hypovolemia. [29]
One of the most common causes of AKI in hospitalized children is Nephrotoxin exposure.[30] Some well-known nephrotoxins are Amphotericin, aminoglycoside, vancomycin, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcineurin inhibitors, cisplatin and methotrexate etc.[29] Doctors must need to be balance the therapeutic benefits versus the

risk for nephrotoxicity. If the use of nephrotoxic medications is mandatory, their dosage or dosing interval should be adjusted and monitored to reduce renal toxicity.

Nutritional support is crucial for improving outcomes in children with AKI. For ill children with AKI, nutritional requirements should be individualized and frequently assessed.[31]

3. Pharmacological treatment

Many researchers conducted investigation regarding medications to prevent and treat AKI. Anti-inflammatory, anti-oxidative and anti-apoptotic interventions are representative examples; however, their yield remains insignificant. Although in certain situations, a few medications have demonstrated effectiveness, but most have yielded negative or conflicting results. The KDIGO guideline recommend NAC to prevent contrast-induced AKI in high-risk patients.[4] However, two large, well-designed studies reported no benefit of N-Acetylcysteine (NAC) in reducing the incidence of contrast- induced AKI.[32] Diuretics are not recommended for the prevention of AKI as their use does not alter outcomes in those with established AKI. It should be used only to control fluid overload. Low-dose dopamine and fenoldopam did not have a positive effect on protection against AKI.[33] To establish the basis for routine clinical use of new medications, additional multicenter, high-quality trials must be considered.

4. RRT and Dialysis

RRT is required when conservative care fails. Children with AKI should be referred for renal replacement therapy (RRT)[34] when they have refractory fluid overload, hyperkalaemia, hyponatraemia, uraemia or acidosis. Continuous hemofiltration/ diafiltraton and/or peritoneal dialysis (PD) are recommended for hemodynamically unstable children with AKI. Intermittent haemodialysis (HD) is suitable for haemodynamically stable patients given the risk of hypotension.[35]

Future perspective

Recently, widely used renal function marker, creatinine, is restricted dueto its late increase in the course of AKI, and its susceptibility to changes by nonrenal factors such as gender, age and muscle mass.[36] In this regard, researchers have been searching new biomarkers that are rapid, sensitive, specific, inexpensive, noninvasive, and unaffected by clinical factors. Some of these are Cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1, N-acetyl- - D-glucosaminidase, interleukin-18, liver-type fatty acid binding protein, cycle arrest markers. Among them, the most widely studied is NGAL. Using NGAL, after post-operative insult in cardiac surgeries in patients, sepsis and contrast use, showed good accuracy for the detection of AKI.[37] These biomarkers are appeared to detect AKI earlier and predict prognosis more accurately than serum creatinine levels. The concept of "Renal Angina" (RA) was also developed to improve the pre-test probability of available biomarkers in 2010, which have some special features that indicate risk for AKI and early clinical signs of renal damage.[38]

The RA concept has been assessed in one large group of critically-ill adult patients. It showed a high sensitivity (92%) associated with the development of AKI.[39] For a better detection of renal angina,an assessment tool called the Renal Angina Index (RAI) has been developed in the pediatric population. To calculate the "Renal Angina Index" (RAI), it is defined by some factors that make the child susceptible to AKI, and early clinical signs of AKI (injury). Each characteristic assigns a score and the score obtained in "risk" is multiplied bythe score obtained in "injury", resulting in the RAI (Table 2).[19]

Table 2. Renal Angina Index calculation.

Risk factor	**Risk**	**Score**
Pediatric ICU admission	Moderate	1
Transplantation	High	3
Ventilation and inotropy	Very High	5
Decrease in CrCL	**%Fluid overload**	
<0	<0-5%	1
1,0-1,49x	5-9,99%	2
1,5-1,99x	10-14,99%	4

The RA probability assessment in AKI appears as good metrics both in children and adults; future research will need to adjust and recalibrate the RA concept, especially in combination with other AKI biomarkers.

Conclusion

Promising studies aimed into how best to define, predict, diagnose, assess, prevent, and manage the care of pediatric patients with AKI and mitigate its effects are still ongoing. Rapid progress over the past few yearshas brought the advances andit can be hoped that the field continues to expand and allow for improved treatment and prevention strategies in the future.

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